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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,224	09/14/2000	David Thomas Grose	1430-252	5556

7590 05/10/2004

Nixon & Vanderhye
8th Floor
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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	20

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,224	GROSE ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 11-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence Comparisons A [redacted] T

DETAILED ACTION

The Office Action dated 4/7/03 has been vacated in favor of this Office Action which provides a search of the prior art for SEQ ID NO:11-17.

1. Formal Matters

A. Claims 1-19 are pending in this application and were subject to restriction in Paper No. 13. In Paper No. 15, filed 8/13/02, Applicants elected Group II and SEQ ID NO:3, with traverse. Applicants argue that this application is a U.S. National Phase of PCT/GB99/00838 and that the principles of unity apply. Applicants argue that Group IV is a process of using the subject matter of Group I such that Groups I, II and IV define a single inventive concept. First, the Examiner apologizes for the previous Examiner's inclusion of claims 8-10 and 18 in Group I. Claim 18 is drawn to the use of a modulator and is not the same inventive concept as a method of using a protein, as recited in claims 15 and 16. Therefore, claims 18 should have been characterized as part of Group IV and not as part of Group IV, which would separate Group IV from Group I. Additionally, claims 8-10 are drawn to human sequences whereas Group I, claims 1-7, 11, 12 and 14-16 are drawn to rat sequences. These are different inventive concepts and, therefore, should be in separate Groups. However, since claims 1-7, 11, 12 and 14-16 (polynucleotide and polypeptide) define a single inventive concept, the Examiner has combined these claims. However, claims 1-19 were subject to another restriction in Paper No. 16, mailed 10/09/02. In Paper No. 17, filed 1/16/03, Applicants elected Group II, claims 8-10 with traverse and argue that a search of all the claims is not undue. This argument has been considered, but is not deemed persuasive. As explained in the restriction, the Groups are independent and distinct since they claim different SEQ ID NOs and a search for one would not necessarily overlap a search of the other. This is the case regarding searching separate nucleotide sequences as well as searching the protein and antibody. Therefore, this restriction is deemed proper and is, therefore, made FINAL.

B. The Information Disclosure Statement, filed 2/9/01, has been entered into the record.

C. The Supplemental Information Disclosure Statement, filed 2/9/01, has been entered into the record.

2. Specification

A. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

B. The specification is objected to since the priority data referencing PCT/GB99/00838 is not present in the first paragraph of the specification.

3. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 8-10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. These claims are directed to polynucleotides of SEQ ID NO:3-17, which are purported to encode a human sodium channel protein. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

Applicants disclose in the specification that SEQ ID NO:3-17 are all fragments of a gene encoding a human sodium channel protein. However, it is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the polynucleotides of the invention encode proteins which have significant sequence similarity to sodium channel proteins (page 3, last paragraph). Based on the structural similarity, the specification asserts that the protein encoded for by SEQ ID NO:3-17 have similar activities. Figure 11 and Example 7 demonstrate that the protein of SEQ ID NO:2 (i.e. rat) is a sodium channel. However, no Figures or Examples show that the protein encoded for by SEQ ID NO:3-17 is a human sodium channel. The assertion that the disclosed proteins have biological activities similar to known sodium channel proteins cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a

small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed polynucleotide and polypeptide of SEQ ID NO:1 and 2 which are only known to be homologous to sodium channel proteins. Therefore, the instant claims are drawn to a polynucleotide and protein which have a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

4. Claim Rejections - 35 USC § 112, first paragraph – lack of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B. Furthermore, even if claim 8-10 possessed utility under 35 USC 101, they would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while then being enabling for the polynucleotides of SEQ ID NO:3-17, does not reasonably provide enablement for polynucleotides which are **"at least 70% identical"** to SEQ ID NO:3-17, or which **"hybridize"** to these SEQ ID NOs. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to claiming all polynucleotides which are "at least 70% identical" to SEQ ID NO:3-17, or those which "hybridize" under stringent conditions to these SEQ ID NOs. These nucleic acid molecules would have one or more nucleic acid substitutions, deletions, insertions and/or additions to the polynucleotide of SEQ ID NO:1 and would encode proteins which have one or more amino acid substitutions, deletions, insertions and/or additions to the protein encoded for by these SEQ ID NOs.

Applicants provide no guidance or working examples of nucleic acid molecules which hybridize to SEQ ID NO:3-17, or which are at least 70% identical to SEQ ID NO:3-17, nor do they provide a *function* of these nucleic acid molecules, or of the proteins which they encode. Applicants have provided no guidance as to what critical bases, or encoded residues, are required to maintain the functional characteristics of the protein of SEQ ID NO:3-17. Furthermore, it is not predictable to one of ordinary skill in the art how to make a functional sodium channel protein comprising polynucleotides which are less than 100% identical to those of SEQ ID NO:3-17.

In summary, the breadth of the claims is excessive with regard to Applicants claiming all nucleic acids which hybridize to, or which are at least 70% identical to, SEQ ID NO:3-17. There is also a lack of guidance and working examples of these nucleic acid molecules and proteins as well as which bases and amino acid residues are critical for protein function. These factors, along with the lack of predictability to one of ordinary skill in the art as to how to make a functional sodium channel protein encoded for other than SEQ ID NO:3-17 leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

5. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. Nucleic acid molecules which **"hybridize"** to, or which are **"at least 70% identical"** to those polynucleotides of SEQ ID NO:3-17 would have one or more nucleic acid substitutions, deletions, insertions and/or additions to said polynucleotides and encode proteins with one or more amino acid substitutions, deletions, insertions and/or additions to the protein encoded for by SEQ ID NO:3-17.

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:3-17, or molecules which hybridize to, or which are 70% identical to, these polynucleotides (which could be at least thousands of molecules) alone are insufficient to describe the genus.

The specification only provides a written description of a rat and human nucleic acid construct. No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical nucleic acid residues which would structurally characterize the genus of nucleic acids encoding the genus of sodium channel proteins claimed, because it is unknown and not described what structurally constitutes any different nucleic acids encoding sodium channel proteins, or nucleic acids encoding sodium channel proteins from any different species, which are further not described, or any different nucleic acid sequence that is "at least 70% identical" to that depicted as SEQ ID NO:3-17; thereby not meeting the written description requirement under 35 USC 112, first paragraph. Therefore, one of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

6. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B. Claim 8 is vague and indefinite since the claim recites "stringent conditions." It is not known what these conditions are. Nucleic acid molecules which hybridize under conditions of "low" stringency would not necessarily hybridize under conditions of "high" stringency. Furthermore, not all conditions of "high" or "low" stringency, for example, are the same. Therefore, it is required that Applicants amend the claims to recite the exact hybridization conditions without using indefinite phrases such as *"for example"* **without adding new matter.** Claims 9 and 10 are also rejected since they depend from claim 8.

7. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

A. Claims 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al. The claims recite a nucleic acid molecule which hybridizes to SEQ ID NO:4 under stringent conditions. Bonaldo et al. teach this nucleic acid molecule (Sequence Comparison A). However, no stringent conditions are recited in the claim. Therefore, due to the numerous areas of 100% overlap between the sequence of Bonaldo and that of SEQ ID NO:4, the nucleic acid of Bonaldo et al. would be expected to

meet this limitation. The artisan would immediately envision the amino acid sequence encoded by this polynucleotide.

B. Claims 8 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Tate et al. The claims recite a nucleic acid molecule which hybridizes to SEQ ID NO:5 under stringent conditions. Tate et al. teach this nucleic acid molecule (Sequence Comparison B). However, no stringent conditions are recited in the claim. Therefore, due to the numerous areas of 100% overlap between the sequence of Tate and that of SEQ ID NO:5, the nucleic acid of Tate would be expected to meet this limitation. The artisan would immediately envision the amino acid sequence encoded by this polynucleotide.

C. Claims 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. The claims recite a nucleic acid molecule which hybridizes to SEQ ID NO:9 under stringent conditions. Hillier et al. teach this nucleic acid molecule (Sequence Comparison C). However, no stringent conditions are recited in the claim. Therefore, due to the numerous areas of 100% overlap between the sequence of Hillier and that of SEQ ID NO:9, the nucleic acid of Hillier would be expected to meet this limitation. The artisan would immediately envision the amino acid sequence encoded by this polynucleotide.

D. Claims 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. The claims recite a nucleic acid molecule which hybridizes to SEQ ID NO:10 under stringent conditions. Hillier et al. teach this nucleic acid molecule (Sequence Comparison D). However, no stringent conditions are recited in the claim. Therefore, due to the numerous areas of 100% overlap between the sequence of Hillier and that of SEQ ID NO:9, the nucleic acid of Hillier would be expected to meet this limitation. The artisan would immediately envision the amino acid sequence encoded by this polynucleotide.

E. Claims 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Dib-Hajj et al. The claims recite a nucleic acid molecule which hybridizes to SEQ ID NO:3-17 under stringent conditions. Dib-Hajj et al. teach these nucleic acid molecules (Sequence Comparison E, G, I-M). However, no stringent conditions are recited in the claim. Therefore, due to the numerous areas of 100% overlap between the sequence of Dib-Hajj and that of SEQ ID NO:3-17, the nucleic acids of Dib-Hajj would be expected to meet this limitation. The artisan would immediately envision the amino acid sequence encoded by this polynucleotide. Due to the length and easy accessibility of the patent, only the first page has been included in this Office Action.

F. Claims 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Au-Young et al. The claims recite a nucleic acid molecule which hybridizes to SEQ ID NO:4, 5 under stringent conditions. Au-Young et al. teach these nucleic acid molecules (Sequence Comparison F, H). However, no stringent conditions are recited in the claim. Therefore, due to the numerous areas of 100% overlap between the sequence of Au-Young and that of SEQ ID NO:4, 5, the nucleic acids of Dib-Hajj would be expected to meet this limitation. The artisan would immediately envision the amino acid sequence encoded by this polynucleotide. Due to the length and easy accessibility of the patent, only the first page has been included in this Office Action.

8. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
October 07, 2003

ROBERT LANDSMAN
PATENT EXAMINER

Sequence Comparison

A

SEQ ID NO:4

```
LOCUS       BM938554                679 bp    mRNA    linear   EST 29-APR-2002
DEFINITION  UI-M-CG0p-bev-f-08-0-UI.r1 NIH_BMAP_Ret4_S2 Mus musculus cDNA clone
            UI-M-CG0p-bev-f-08-0-UI 5', mRNA sequence.
ACCESSION   BM938554
VERSION     BM938554.1  GI:19397706
KEYWORDS    EST.
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 679)
  AUTHORS   Bonaldo,M.F., Lennon,G. and Soares,M.B.
  TITLE     Normalization and subtraction: two approaches to facilitate gene
            discovery
  JOURNAL   Genome Res. 6 (9), 791-806 (1996)
  MEDLINE   97044477
   PUBMED   8889548
COMMENT     Contact: Chin, H
            National Institute of Mental Health
            6001 Executive Blvd. Room 7N-7190, MSC 9643, Bethesda, MD
            20892-9643, USA
            Tel: 301 443 1706
            Fax: 301 443 9890
            Email: mEST@mail.nih.gov
            Tissue Procurement: Dr. Xin-Yuan Fu, Yale University School of
            Medicine
             cDNA Library preparation: Dr. M. Bento Soares, Univeristy of Iowa
             cDNA Library Arrayed by: Dr. M. Bento Soares, Univeristy of Iowa
             DNA Sequencing by: Dr. M. Bento Soares, Univeristy of Iowa
             Clone Distribution: Researchers may obtain clones from Research
            Genetics (www.resgen.com).
            Seq primer: M13 REVERSE.
FEATURES             Location/Qualifiers
     source          1. .679
                     /organism="Mus musculus"
                     /mol_type="mRNA"
                     /strain="C57BL/6J"
                     /db_xref="taxon:10090"
                     /clone="UI-M-CG0p-bev-f-08-0-UI"
                     /lab_host="DH10B (Life Technologies)"
                     /clone_lib="NIH_BMAP_Ret4_S2"
                     /note="Vector: pT7T3D-Pac (Pharmacia) with a modified
                     polylinker; Site_1: Not I; Site_2: Eco RI; The
                     NIH_BMAP_Ret4_S2 library is a subtracted library,
                     ultimately derived from mouse retina tissue libraries at
                     various stages of development. For a detailed description
                     of the library from which this clone was derived, please
                     visit our web site at brainest.eng.uiowa.edu. The tissue
                     for this library was contributed by Dr. Xin-Yuan Fu, Yale
                     University School of Medicine"
BASE COUNT      151 a    216 c    139 g    172 t      1 others
ORIGIN
```

```
  Query Match           42.6%;  Score 59.6;  DB 12;  Length 679;
  Best Local Similarity  68.0%;  Pred. No. 1.5e-07;
  Matches   83;  Conservative    0;  Mismatches   39;  Indels    0;  Gaps    0;

Qy          4 TCTGTGAAGAAGCTGGTCAACGTGATTATCCTCACCTTCTTTTGCCTCAGCATCTTTGCC 63
              |||||||||||||||    ||||||| ||||| ||  | || ||||| ||  |||| |||
Db        224 TCTGTGAAGAAGCTGTCAGACGTGATGATCCTGACGGTGTTCTGCCTGAGTGTCTTCGCC 165

Qy         64 CTGGTAGGTCAGCAGCTCTTCATGGGAAGTCTGAACCTGAAATGCATCTCGAGGGACTGT 123
              ||| | || | ||||||||||||||| |  ||       || ||  ||  | ||  |
Db        164 CTGATTGGCCTGCAGCTCTTCATGGGGAACCTTCGAAACAAGTGTGTCGTGTGGCCCATA 105

Qy        124 AA 125
              ||
Db        104 AA 103
```

Sequence Comparison B

SEQ ID NO:5

```
LOCUS       RNO237852               5849 bp    mRNA    linear   ROD 03-MAY-1999
DEFINITION  Rattus norvegicus mRNA for voltage-gated sodium channel alpha
            subunit.
ACCESSION   AJ237852
VERSION     AJ237852.1  GI:4741728
KEYWORDS    alpha subunit; sns2 gene; voltage-gated sodium channel.
SOURCE      Rattus norvegicus (Norway rat)
  ORGANISM  Rattus norvegicus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae;
            Rattus.
REFERENCE   1
  AUTHORS   Tate,S., Benn,S., Hick,C., Trezise,D., John,V., Mannion,R.J.,
            Costigan,M., Plumpton,C., Grose,D., Gladwell,Z., Kendall,G.,
            Dale,K., Bountra,C. and Woolf,C.J.
  TITLE     Two sodium channels contribute to the TTX-R sodium current in
            primary sensory neurons
  JOURNAL   Nat. Neurosci. 1 (8), 653-655 (1998)
  MEDLINE   99212311
   PUBMED   10196578
REFERENCE   2  (bases 1 to 5849)
  AUTHORS   Tate,S.N.
  TITLE     Direct Submission
  JOURNAL   Submitted (28-APR-1999) Tate S.N., Molecular Pharmacology,
            GlaxoWellcome Research and Development, Medecines Research Centre,
            Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UNITED
            KINGDOM
FEATURES             Location/Qualifiers
     source          1. .5849
                     /organism="Rattus norvegicus"
                     /mol_type="mRNA"
                     /strain="Sprague-Dawley"
                     /db_xref="taxon:10116"
                     /tissue_type="dorsal root ganglia"
     gene            1. .5849
                     /gene="sns2"
     CDS             1. .5298
                     /gene="sns2"
                     /codon_start=1
                     /product="voltage-gated sodium channel alpha subunit"
                     /protein_id="CAB41850.1"
                     /db_xref="GI:4741729"
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BASE COUNT     1459 a   1458 c   1423 g   1509 t
ORIGIN

  Query Match             54.0%;  Score 125.2;  DB 10;  Length 5849;
  Best Local Similarity   73.4%;  Pred. No. 4e-23;
  Matches  160;  Conservative    0;  Mismatches   58;  Indels    0;  Gaps    0;

Qy         14 AACCCGGAAGCTTATGACCATTGCTTTGAAAAGAAAGAAAATTCACCTGAATTCAAAATG 73
              ||||| | | |  |  | ||||||||||||||| || || ||      || |||| ||||
Db        862 AACCCTGCATCCAACAAGGATTGCTTTGAAAAGGAAAAAGATAGCGAAGACTTCATAATG 921

Qy         74 TGTGGCATCTGGATGGGTAACAGTGCCTGTTCCATACAATATGAATGTAAGCACACCAAA 133
              ||||| | |||| | || | ||| |||||  |||     | |   ||  |  | |||| |
Db        922 TGTGGTACCTGGCTCGGCAGCAGACCCTGTCCCAATGGTTCTACGTGCGATAAAACCACA 981

Qy        134 ATTAATCCTGACTATAATTATACGAATTTTGACAACTTTGGCTGGTCTTTTCTTGCCATG 193
              | || || ||| |||||||||| || ||||||||||||||||||||| ||||| ||||||
Db        982 TTGAACCCAGACAATAATTATACAAAGTTTGACAACTTTGGCTGGTCCTTTCTCGCCATG 1041

Qy        194 TTCCGGCTGATGACCCAAGATTCCTGGGAGAAGCTTTA 231
              |||||| | ||||| ||||| |||||||||| ||||||
Db       1042 TTCCGGGTTATGACTCAAGACTCCTGGGAGAGGCTTTA 1079
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SEQ ID NO:9 Sequence Comparison C

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LOCUS       AA446878                 499 bp    mRNA    linear   EST 03-JUN-1997
DEFINITION  zw90c04.s1 Soares_total_fetus_Nb2HP8_9w Homo sapiens cDNA clone
            IMAGE:784230 3' similar to gb:M81758 SODIUM CHANNEL PROTEIN,
            SKELETAL MUSCLE ALPHA-SUBUNIT (HUMAN);, mRNA sequence.
ACCESSION   AA446878
VERSION     AA446878.1  GI:2159543
KEYWORDS    EST.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 499)
  AUTHORS   Hillier,L., Allen,M., Bowles,L., Dubuque,T., Geisel,G., Jost,S.,
            Kucaba,T., Lacy,M., Le,N., Lennon,G., Marra,M., Martin,J., Moore,B.
            , Schellenberg,K., Steptoe,M., Tan,F., Theising,B., White,Y., Wylie
            ,T., Waterston,R. and Wilson,R.
  TITLE     WashU-Merck EST Project 1997
  JOURNAL   Unpublished
COMMENT     Contact: Wilson RK
            Washington University School of Medicine
            4444 Forest Park Parkway, Box 8501, St. Louis, MO 63108
            Tel: 314 286 1800
            Fax: 314 286 1810
            Email: est@watson.wustl.edu
            This clone is available royalty-free through LLNL ; contact the
            IMAGE Consortium (info@image.llnl.gov) for further information.
            Possible reversed clone: polyT not found
            Seq primer: -41m13 fwd. ET from Amersham
            High quality sequence stop: 392.
FEATURES             Location/Qualifiers
     source          1. .499
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="GDB:5981848"
                     /db_xref="taxon:9606"
                     /clone="IMAGE:784230"
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/dev_stage="8-9 weeks"
/lab_host="DH10B"
/clone_lib="Soares_total_fetus_Nb2HF8_9w"
/note="Vector: pT7T3D-Pac (Pharmacia) with a modified polylinker; Site_1: Not I; Site_2: Eco RI; 1st strand cDNA was prepared from mRNA obtained from pooled 8-9 week (total) fetus material with a Not I - oligo(dT) primer [5' TGTTACCAATCTGAAGTGGGAGCGGCCGCTTAATTTTTTTTTTTTTTT 3']. Double-stranded cDNA was ligated to Eco RI adaptors (Pharmacia), digested with Not I and cloned into the Not I and Eco RI sites of the modified pT7T3 vector. Library went through one round of normalization, and was constructed by Bento Soares and M. Fatima Bonaldo. "

BASE COUNT 160 a 110 c 100 g 129 t
ORIGIN

Query Match 71.4%; Score 239.2; DB 9; Length 499;
Best Local Similarity 94.1%; Pred. No. 9.6e-60;
Matches 303; Conservative 0; Mismatches 12; Indels 7; Gaps 5;

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Qy        15 CTTAACTGGCTTTTCT--CCGTTTTCGTTCGTCGCTTTTTCTACAGCTCA-GGTCTTCAA 71
             |||||||||||||||  |  ||||  ||  |  |||||||||||||||| |||||||||
Db       478 CTTAACTGGCTTTTCTTCCATTTTTGTTTGTTGTCTTTTTCTACAGCTCAGGGTCTTCAA 419

Qy        72 GT--ACCAAATCCTGGCCAACTTTGAACACACTAATTAAGATAATCCGGCAACTCTCGTC 129
             ||  ||||||||||||||||||||||||||||||||||||||||| |||||||||| |||
Db       418 GTTAGCCAAATCCTGGCCAACTTTGAACACACTAATTAAGATAAT-CGGCAACTCT-GTC 361

Qy       130 GGAGCCCTTGGAAGCCTGACTGTGGTCCTGGTCATTGTGATCTTTATTTTCTCAGTAGTT 189
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       360 GGAGCCCTTGGAAGCCTGACTGTGGTCCTGGTCATTGTGATCTTTATTTTCTCAGTAGTT 301

Qy       190 GGCATGCAGCTTTTTGGCCGTAGCTTCAATTCCCAAAAGAGTCCAAAACTCTGTAACCCG 249
             |||||||||||||||||||| ||||||||||||||||||||||||||||||||||||||
Db       300 GGCATGCAGCTTTTTGGCCGCAGCTTCAATTCCCAAAAGAGTCCAAAACTCTGTAACCCG 241

Qy       250 ACAGGCCCGACAGTCTCATGTTTACGGCACTGGCACATGGGGGATTTCTGGCACTCCTTC 309
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       240 ACAGGCCCGACAGTCTCATGTTTACGGCACTGGCACATGGGGGATTTCTGGCACTCCTTC 181

Qy       310 CTAGTGGTATCGCGCATCCTCT 331
             |||||||||| ||||||||||
Db       180 CTAGTGGTATTCCGCATCCTCT 159
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SEQ ID NO:10 Sequence Comparism D

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LOCUS       AA634923                382 bp    mRNA    linear   EST 06-MAR-1998
DEFINITION  ab28g06.r1 Stratagene lung (#937210) Homo sapiens cDNA clone
            IMAGE:842170 5', mRNA sequence.
ACCESSION   AA634923
VERSION     AA634923.1  GI:2558137
KEYWORDS    EST.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 382)
  AUTHORS   Hillier,L., Allen,M., Bowles,L., Dubuque,T., Geisel,G., Jost,S.,
            Krizman,D., Kucaba,T., Lacy,M., Le,N., Lennon,G., Marra,M., Martin
            ,J., Moore,B., Schellenberg,K., Steptoe,M., Tan,F., Theising,B.,
            White,Y., Wylie,T., Waterston,R. and Wilson,R.
```

```
  TITLE     WashU-NCI human EST Project
  JOURNAL   Unpublished
COMMENT     Contact: Wilson RK
            Washington University School of Medicine
            4444 Forest Park Parkway, Box 8501, St. Louis, MO 63108
            Tel: 314 286 1800
            Fax: 314 286 1810
            Email: est@watson.wustl.edu
            This clone is available royalty-free through LLNL ; contact the
            IMAGE Consortium (info@image.llnl.gov) for further information.
            Insert Length: 1063    Std Error: 0.00
            Seq primer: -28m13 rev1 ET from Amersham
            High quality sequence stop: 381.
FEATURES             Location/Qualifiers
     source          1. .382
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                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /clone="IMAGE:842170"
                     /sex="male"
                     /dev_stage="72 years"
                     /lab_host="SOLR cells (kanamycin resistant)"
                     /clone_lib="Stratagene lung (#937210)"
                     /note="Organ: lung; Vector: pBluescript SK-; Site_1: EcoRI
                     ; Site_2: XhoI; Cloned unidirectionally.  Primer: Oligo
                     dT. normal lung.  Average insert size: 1.0 kb; Uni-ZAP XR
                     Vector; ~5' adaptor sequence: 5' GAATTCGGCACGAG 3' ~3'
                     adaptor sequence: 5' CTCGAGTTTTTTTTTTTTTTTT 3'"
BASE COUNT       93 a     87 c     79 g    123 t
ORIGIN

  Query Match             13.6%;  Score 35.4;  DB 9;  Length 382;
  Best Local Similarity   56.4%;  Pred. No. 7.9;
  Matches   66;  Conservative    0;  Mismatches   51;  Indels    0;  Gaps    0;

Qy          9 CAAAGACCCTGGGCGTCAGGCATGATTGGACTTGGTTGGCACCACTTGCGGAGGAGGAAG 68
              || | || | || | ||||       |||  | |||||||| || |||    |   |||
Db        138 CAGAAACACAGGCCTTCAGCTCACGCTGGGGTCGGTTGGCAGCAGTTGTATGGATAGAAA 197

Qy         69 ATGACGTTGAATTTTCTGGTGAAGATAATGCACAGCGCATCACACAACCTGAGCCTG 125
              | | | |||  ||    | ||||     ||||||| || |  ||||  |  | || |
Db        198 AGGGCATTGTGTTCAGGGCTGAATCCTCTGCACAGTGCCTTCCACATACATAACCCG 254
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SEQ ID NO:3 E

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; Sequence 41, Application US/09354147C
; Patent No. 6573067
; GENERAL INFORMATION:
;  APPLICANT: Dib-Hajj, Sulayman
;  APPLICANT:  Waxman, Stephen G.
;  TITLE OF INVENTION: Modulation of Sodium Channels in Dorsal Root Ganglia
;  FILE REFERENCE: 44574-5004-01-US
;  CURRENT APPLICATION NUMBER: US/09/354,147C
;  CURRENT FILING DATE:  1999-07-16
;  PRIOR APPLICATION NUMBER: US 60/072,990
;  PRIOR FILING DATE: 1998-01-29
;  PRIOR APPLICATION NUMBER: US 60/109,402
;  PRIOR FILING DATE: 1998-11-20
;  PRIOR APPLICATION NUMBER: PCT/US99/02008
;  PRIOR FILING DATE: 1999-01-29
;  NUMBER OF SEQ ID NOS: 44
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 41
;   LENGTH: 5860
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (31)..(5403)
;   OTHER INFORMATION: full length cDNA sequence for human NaN
US-09-354-147C-41

  Query Match            68.4%;  Score 204.4;  DB 4;  Length 5860;
  Best Local Similarity  96.9%;  Pred. No. 8.7e-62;
  Matches  219;  Conservative    0;  Mismatches    6;  Indels    1;  Gaps    1;

Qy         73 GGGTGAAGATGGATGACAGATGCTACCCAGTAATCTTTCCAGATGAGCGGAATTTCCGCC 132
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 GGGTGAAGATGGATGACAGATGCTACCCAGTAATCTTTCCAGATGAGCGGAATTTCCGCC 82

Qy        133 CCTTCACTTCCGACTCTCTGGCTGCAATTGAGAAGCGGATTGCCATCCAAAAGGAGAAAA 192
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 CCTTCACTTCCGACTCTCTGGCTGCAATTGAGAAGCGGATTGCCATCCAAAAGGAGAAAA 142

Qy        193 AGAAGTCTAAAGACCAGACAGGAGAAGTACCCCAGCCTCAACCTCAGCTTGACCTAAAGG 252
              |||||||||||||||||||||||||||||||||||| ||||||||||||||||||||
Db        143 AGAAGTCTAAAGACCAGACAGGAGAAGTACCCCAGCCTCGGCCTCAGCTTGACCTAAAGG 202

Qy        253 CCTCCAGGAAGTTGCCCAA-CTCTATGGCGACAATCCTCGGAGGCT 297
              |||||||||||||||||| |||||||||||| ||||||   |||
Db        203 CCTCCAGGAAGTTGCCCAAGCTCTATGGCGACATTCCTCGTGAGCT 248
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SEQ ID NO:4

F

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; Sequence 93, Application US/09016434
; Patent No. 6500938
;  GENERAL INFORMATION:
;    APPLICANT:  Janice Au-Young
;    APPLICANT:  Jeffrey J. Seilhamer
;    TITLE OF INVENTION:  COMPOSITION FOR THE DETECTION OF SIGNALING
;    TITLE OF INVENTION:  PATHWAY GENE EXPRESSION
;    NUMBER OF SEQUENCES:  1490
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  INCYTE PHARMACEUTICALS, INC.
;      STREET:  3174 PORTER DRIVE
;      CITY:  PALO ALTO
;      STATE:  CALIFORNIA
;      COUNTRY:  USA
;      ZIP:  94304
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  Word Perfect 6.1 for Windows/MS-DOS 6.2
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/09/016,434
;      FILING DATE:  HEREWITH
;      CLASSIFICATION:
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;      CLASSIFICATION:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Zeller, Karen J.
;      REGISTRATION NUMBER:  37,071
;      REFERENCE/DOCKET NUMBER:  PA-0002 US
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (650) 855-0555
;      TELEFAX:  (650) 845-4166
;  INFORMATION FOR SEQ ID NO:  93:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  264 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    IMMEDIATE SOURCE:
;      LIBRARY:  LUNGTUT02
;      CLONE:  1238311
US-09-016-434-93

  Query Match           100.0%;  Score 140;  DB 4;  Length 264;
  Best Local Similarity  100.0%;  Pred. No. 1.6e-34;
  Matches  140;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CGCTCTGTGAAGAAGCTGGTCAACGTGATTATCCTCACCTTCTTTTGCCTCAGCATCTTT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 CGCTCTGTGAAGAAGCTGGTCAACGTGATTATCCTCACCTTCTTTTGCCTCAGCATCTTT 60

Qy         61 GCCCTGGTAGGTCAGCAGCTCTTCATGGGAAGTCTGAACCTGAAATGCATCTCGAGGGAC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GCCCTGGTAGGTCAGCAGCTCTTCATGGGAAGTCTGAACCTGAAATGCATCTCGAGGGAC 120

Qy        121 TGTAAAAATATCAGTAACCC 140
              ||||||||||||||||||||
Db        121 TGTAAAAATATCAGTAACCC 140
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SEQ ID NO:5

G

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; Sequence 41, Application US/09354147C
; Patent No. 6573067
; GENERAL INFORMATION:
US-09-354-147C-41

  Query Match             100.0%;  Score 232;  DB 4;  Length 5860;
  Best Local Similarity   100.0%;  Pred. No. 1.1e-61;
  Matches  232;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TAAAAATATCAGTAACCCGGAAGCTTATGACCATTGCTTTGAAAAGAAAGAAAATTCACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        894 TAAAAATATCAGTAACCCGGAAGCTTATGACCATTGCTTTGAAAAGAAAGAAAATTCACC 953

Qy         61 TGAATTCAAAATGTGTGGCATCTGGATGGGTAACAGTGCCTGTTCCATACAATATGAATG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        954 TGAATTCAAAATGTGTGGCATCTGGATGGGTAACAGTGCCTGTTCCATACAATATGAATG 1013

Qy        121 TAAGCACACCAAAATTAATCCTGACTATAATTATACGAATTTTGACAACTTTGGCTGGTC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1014 TAAGCACACCAAAATTAATCCTGACTATAATTATACGAATTTTGACAACTTTGGCTGGTC 1073

Qy        181 TTTTCTTGCCATGTTCCGGCTGATGACCCAAGATTCCTGGGAGAAGCTTTAT 232
              |||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1074 TTTTCTTGCCATGTTCCGGCTGATGACCCAAGATTCCTGGGAGAAGCTTTAT 1125


RESULT 3
US-09-016-434-93
; Sequence 93, Application US/09016434
; Patent No. 6500938
US-09-016-434-93

  Query Match             61.2%;  Score 142;  DB 4;  Length 264;
  Best Local Similarity   100.0%;  Pred. No. 1.5e-34;
  Matches  142;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TAAAAATATCAGTAACCCGGAAGCTTATGACCATTGCTTTGAAAAGAAAGAAAATTCACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        123 TAAAAATATCAGTAACCCGGAAGCTTATGACCATTGCTTTGAAAAGAAAGAAAATTCACC 182

Qy         61 TGAATTCAAAATGTGTGGCATCTGGATGGGTAACAGTGCCTGTTCCATACAATATGAATG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        183 TGAATTCAAAATGTGTGGCATCTGGATGGGTAACAGTGCCTGTTCCATACAATATGAATG 242

Qy        121 TAAGCACACCAAAATTAATCCT 142
              ||||||||||||||||||||||
Db        243 TAAGCACACCAAAATTAATCCT 264
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H

SEQ ID NO:6

I

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; Sequence 6, Application US/09354147C
; Patent No. 6573067
  Query Match             62.3%;  Score 112.2;  DB 4;  Length 3701;
  Best Local Similarity   92.6%;  Pred. No. 7e-29;
  Matches  162;  Conservative    0;  Mismatches    8;  Indels    5;  Gaps    4;

Qy          7 GGGTCTACTCAGTCTTCTTCTTCATTGTGGTCATTTTCCTGGGGCTCCCTTCTACCTGAT 66
              || |||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        521 GGCTCTACTCAGTCTTCTTCTTCATTGTGGTCATTTTCCTGGGCT--CCTTCTACCTGAT 578
```

```
Qy         67 TAACTTAAACCCTGGCTGTTGTTACCATGGGCATATGAGGAGCCGAACAAGAATGTAGCT 126
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        579 TAACTT-AACCCTGGCTGTTGTTACCAT-GGCATATGAGGAGCAGAACAAGAATGTAGCT 636

Qy        127 GCAGAGATAGAGGCCCAGGAAAAGATG-TTCAGGAAGCCCAGCAGCTGGTTAAAG 180
              ||||||||||||||| |||||||||||| |||||||||||||||||||| | || |
Db        637 GCAGAGATAGAGGCCAAGGAAAAGATGTTTCAGGAAGCCCAGCAGCTGTTAAAGG 691
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SEQ ID NO:7

J

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; Sequence 41, Application US/09354147C
; Patent No. 6573067
  Query Match             49.1%;  Score 88.4;  DB 4;  Length 5860;
  Best Local Similarity   98.9%;  Pred. No. 3e-19;
  Matches   89;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy          1 TATCACTGGACCACTTTGATGAGCATGGAGATCCTCTCCAAAGGCAGAGAGCACTGAGTG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1544 TATCACTGGACCACTTTGATGAGCATGGAGATCCTCTCCAAAGGCAGAGAGCACTGAGTG 1603

Qy         61 TTGTCAGCATCCTCACCATCACCATGAAGG 90
              ||||||||||||||||||||||||||||||
Db       1604 CTGTCAGCATCCTCACCATCACCATGAAGG 1633
```

SEQ ID NO:8

K

```
; Sequence 6, Application US/09354147C
; Patent No. 6573067
  Query Match             65.2%;  Score 195;  DB 4;  Length 3701;
  Best Local Similarity   90.5%;  Pred. No. 2.8e-55;
  Matches  220;  Conservative    0;  Mismatches   20;  Indels    3;  Gaps    1;

Qy         57 GAACAAGAAAAATCACAAGAGCCTTGTCTCCCTTGTGGAGAAAACCTGGCATCCAAGTAC 116
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1006 GAACAAGAAAAATCACAAGAGCCTTGTCTCCCTTGTGGAGAAAACCTGGCATCCAAGTAC 1065

Qy        117 CTCGTGTGGAACTGTTGCCCCCAGTGGCTGTGCGTAAAGAAGGTCCTGAGAACCGTCATG 176
              ||||||||||||||||||||||||||||||||||| |||||||||||||||| || |||
Db       1066 CTCGTGTGGAACTGTTGCCCCCAGTGGCTGTGCGTTAAGAAGGTCCTGAGAACTGTGATG 1125

Qy        177 ACGGTCCCGTTTACTGAGCTGGACATCACGATCTGCATCATCATCAACACAGACTTCTTG 236
              || | |||||||||||||||| |||||| |||||||||||||||||| | ||||||||
Db       1126 ACTGACCCGTTTACTGAGCTGGCCATCACCATCTGCATCATCATCAACACTGTCTTCTTG 1185

Qy        237 GACATGGAGCATCACAAGATGTAAGGCAACGTATTGGAGACGATGTTGAATATAGGGCAG 296
              | |||||||||||||||||| | | ||     || |||| |||||||||||||||| |
Db       1186 GCCATGGAGCATCACAAGATGGAGGCCA---GTTTTGAGAAGATGTTGAATATAGGGAAT 1242

Qy        297 TAG 299
              | |
Db       1243 TTG 1245
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SEQ ID NO:9

L

; Sequence 6, Application US/09354147C
; Patent No. 6573067
Query Match 68.6%; Score 229.8; DB 4; Length 3701;
Best Local Similarity 98.4%; Pred. No. 3.7e-71;
Matches 253; Conservative 0; Mismatches 2; Indels 2; Gaps 2;

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Qy        75 CCAAATCCTGGCCAACTTTGAACACACTAATTAAGATAATCCGGCAACTCTCGTCGGAGC 134
             ||||||||||||||||||||||||||||||||||||||| |||||||||| ||||||||
Db      1445 CCAAATCCTGGCCAACTTTGAACACACTAATTAAGATAAT-CGGCAACTCT-GTCGGAGC 1502

Qy       135 CCTTGGAAGCCTGACTGTGGTCCTGGTCATTGTGATCTTTATTTTCTCAGTAGTTGGCAT 194
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1503 CCTTGGAAGCCTGACTGTGGTCCTGGTCATTGTGATCTTTATTTTCTCAGTAGTTGGCAT 1562

Qy       195 GCAGCTTTTTGGCCGTAGCTTCAATTCCCAAAAGAGTCCAAAACTCTGTAACCCGACAGG 254
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1563 GCAGCTTTTTGGCCGTAGCTTCAATTCCCAAAAGAGTCCAAAACTCTGTAACCCGACAGG 1622

Qy       255 CCCGACAGTCTCATGTTTACGGCACTGGCACATGGGGGATTTCTGGCACTCCTTCCTAGT 314
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1623 CCCGACAGTCTCATGTTTACGGCACTGGCACATGGGGGATTTCTGGCACTCCTTCCTAGT 1682

Qy       315 GGTATCGCGCATCCTCT 331
             ||||| ||||||||||
Db      1683 GGTATTCCGCATCCTCT 1699
```

SEQ ID NO:10

M

; Sequence 6, Application US/09354147C
; Patent No. 6573067
Query Match 51.3%; Score 134; DB 4; Length 3701;
Best Local Similarity 100.0%; Pred. No. 6.1e-36;
Matches 134; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy         1 CTCTGTACCAAAGACCCTGGGCGTCAGGCATGATTGGACTTGGTTGGCACCACTTGCGGA 60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2106 CTCTGTACCAAAGACCCTGGGCGTCAGGCATGATTGGACTTGGTTGGCACCACTTGCGGA 2165

Qy        61 GGAGGAAGATGACGTTGAATTTTCTGGTGAAGATAATGCACAGCGCATCACACAACCTGA 120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2166 GGAGGAAGATGACGTTGAATTTTCTGGTGAAGATAATGCACAGCGCATCACACAACCTGA 2225

Qy       121 GCCTGAACAACAGG 134
             ||||||||||||||
Db      2226 GCCTGAACAACAGG 2239
```

SEQ ID NO:11

; Patent No. 6573067
; GENERAL INFORMATION:
; APPLICANT: Dib-Hajj, Sulayman
; APPLICANT: Waxman, Stephen G.

US-09-354-147C-6

Query Match 42.0%; Score 90.2; DB 4; Length 3701;
Best Local Similarity 96.8%; Pred. No. 3.7e-21;
Matches 92; Conservative 0; Mismatches 3; Indels 0; Gaps 0;

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Qy        81 AGAAGTCTGATGTTACCAGTATACTATCAGAATGTAGCACCATTGATCTTCAGGATGGCT 140
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2351 AGAAGTCTGATGTTACCAGTATACTATCAGAATGTAGCACCATTGATCTTCAGGATGGCT 2410

Qy       141 TTGGATGGTTACCTGAGATGGTTCCCAAAGAAAAA 175
             |||||||||||||||||||||||||||||| |  ||
Db      2411 TTGGATGGTTACCTGAGATGGTTCCCAAAAAGCAA 2445
```

SEQ ID NO:12

; Patent No. 6573067
; GENERAL INFORMATION:
; APPLICANT: Dib-Hajj, Sulayman
; APPLICANT: Waxman, Stephen G.

Query Match 13.5%; Score 46.8; DB 4; Length 3701;
Best Local Similarity 88.1%; Pred. No. 6.8e-06;
Matches 74; Conservative 0; Mismatches 7; Indels 3; Gaps 2;

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Qy        46 TAACTTAATGGAATT--AGAACCTTCCGGATCTACGAGCACTGAGGCCTC-TCGTGCGCT 102
             |||||||||||||||  ||  | | | |  |||||||||||||||||||| |||||||||
Db      2817 TAACTTAATGGAATTGAAGTCCTTCCGGACTCTACGAGCACTGAGGCCTCTTCGTGCGCT 2876

Qy       103 GTCCCAGTTTGAAGGAATGAAGGT 126
             ||||||||||||||||||||||||
Db      2877 GTCCCAGTTTGAAGGAATGAAGGT 2900
```

SEQ ID NO:13

; Patent No. 6573067
; GENERAL INFORMATION:
; APPLICANT: Dib-Hajj, Sulayman
; APPLICANT: Waxman, Stephen G.
US-09-354-147C-6

Query Match 48.3%; Score 107.8; DB 4; Length 3701;
Best Local Similarity 96.0%; Pred. No. 2.5e-23;
Matches 143; Conservative 0; Mismatches 2; Indels 4; Gaps 3;

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Qy        52 AAGGTGGTGGTCAATGCTCTCATAGGTGCCATACCTCCCATTCCTGAATGTTTTGCTTGT 111
             |||||||||||||||||||||||||||||||||||||||| ||||| ||||||||||||||||
Db      2896 AAGGTGGTGGTCAATGCTCTCATAGGTGCCATACCTGCCATT-CTGAATGTTTTGCTTGT 2954
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Qy        112 CTGCCTCATTTTCTGGCTCGTATTTTGTATTCTGGGAGTATACTTCCTTTTCCTGGAAAA 171
              ||||||||||||||||||||||||||||||||||||||||||||||||  ||| ||||||||
Db       2955 CTGCCTCATTTTCTGGCTCGTATTTTGTATTCTGGGAGTATACTTC--TTTTCTGGAAAA 3012

Qy        172 TTTGGGAAATGCATTCAATGGAACAGACT 200
              |||||||||||||||| ||||||||||||
Db       3013 TTTGGGAAATGCATT-AATGGAACAGACT 3040
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SEQ ID NO:14

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; Patent No. 6573067
; GENERAL INFORMATION:
;  APPLICANT: Dib-Hajj, Sulayman
;  APPLICANT:  Waxman, Stephen G.
US-09-354-147C-6

  Query Match             19.3%;  Score 47;  DB 4;  Length 3701;
  Best Local Similarity   90.9%;  Pred. No. 1.5e-06;
  Matches   50;  Conservative    0;  Mismatches    5;  Indels    0;  Gaps    0;

Qy         36 GGCACAATTTAAGGGCTGGATGGATATCGTTTATGCAGCTGTTGATTCCACAGAG 90
              ||||  |||||||||||||||||||||  | ||||||||||||||||||||||||
Db       3162 GGCAACATTTAAGGGCTGGATGGATATTATATATGCAGCTGTTGATTCCACAGAG 3216
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SEQ ID NO:15

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; Patent No. 6573067
; GENERAL INFORMATION:
;  APPLICANT: Dib-Hajj, Sulayman
;  APPLICANT:  Waxman, Stephen G.
US-09-354-147C-6

  Query Match             32.9%;  Score 134.4;  DB 4;  Length 3701;
  Best Local Similarity   90.1%;  Pred. No. 1.2e-26;
  Matches  155;  Conservative    0;  Mismatches   16;  Indels    1;  Gaps    1;

Qy        202 ATTTCTAACAGAAAGAACAACAGCCAGAGTTTGAGAGCAATTCACTCGGTTACATTT-CT 260
              |||  |  |||||||||||||||||||||||||||||||||||||||||||||||| ||
Db       3206 ATTCCACAGAGAAAGAACAACAGCCAGAGTTTGAGAGCAATTCACTCGGTTACATTTACT 3265

Qy        261 TCGTAGTCTTTATCATCTTTGGCTCATTCTTCACTCTGAATCTCTTCATTGGCGTTATCA 320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3266 TCGTAGTCTTTATCATCTTTGGCTCATTCTTCACTCTGAATCTCTTCATTGGCGTTATCA 3325

Qy        321 TTGACAACTTCAACCAACAGCAGAAAAAGATAAGTATCTGGGTTGTCTTGAT 372
              |||||||||||||||||||||||||||||| || ||  |   |   | || ||
Db       3326 TTGACAACTTCAACCAACAGCAGAAAAAGTTAGGTGGCCAAGACATTTTTAT 3377
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SEQ ID NO:16

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; Patent No. 6573067
; GENERAL INFORMATION:
; APPLICANT: Dib-Hajj, Sulayman
; APPLICANT: Waxman, Stephen G.
US-09-354-147C-41

Query Match 27.9%; Score 163.4; DB 4; Length 5860;
Best Local Similarity 93.7%; Pred. No. 4.1e-39;
Matches 192; Conservative 0; Mismatches 11; Indels 2; Gaps 2;

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Qy        70 TACCTAAACCATGATTGGCTTGATGGCCTAAATATACAACCAACCCCAAAGCCATGGAAT 129
             || |  || ||||||| || ||||||| ||  |||||||||| |||||||||||| |||
Db      4158 TATCCTAAACATGATTAGCATGATGGCTGAATCATACAACCAA-CCCAAAGCCATGAAAT 4216

Qy       130 CCATCCTTGACCATCTCCAACTGGGTCTTTGTGGTCATCTTTACGTTAGAATGTCTCATC 189
             ||||||||||||||| ||||||||||||||||||||||||||||||||||||||||||||
Db      4217 CCATCCTTGACCATCT-CAACTGGGTCTTTGTGGTCATCTTTACGTTAGAATGTCTCATC 4275

Qy       190 AAAATCTTTGCTTTGAGGCAATACTACTTCACCAATGGCTGGAATTTATTTGACTGTGTG 249
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      4276 AAAATCTTTGCTTTGAGGCAATACTACTTCACCAATGGCTGGAATTTATTTGACTGTGTG 4335

Qy       250 GTCGTGCTTCTTTCCATTGTTAGTA 274
             |||||||||||||||||||||||||
Db      4336 GTCGTGCTTCTTTCCATTGTTAGTA 4360
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SEQ ID NO:17

T

; Patent No. 6573067
; GENERAL INFORMATION:
; APPLICANT: Dib-Hajj, Sulayman
; APPLICANT: Waxman, Stephen G.
US-09-354-147C-41

Query Match 90.0%; Score 200.6; DB 4; Length 5860;
Best Local Similarity 97.7%; Pred. No. 1.5e-57;
Matches 214; Conservative 0; Mismatches 4; Indels 1; Gaps 1;

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Qy         5 CAAGGTGGACCAAAATGACTTGGGAAAACGGGCCTCATTCACCACTCCAGACTCTTTGCA 64
             | | |  |||||||||||||| ||||||||||||||||||||||||||||||||||||||
Db      5295 CCAAGGTGACCAAAATGACTT-GGAAAACGGGCCTCATTCACCACTCCAGACTCTTTGCA 5353

Qy        65 ATGGAGACTTGTCTAGCTTTGGGGTGGCCAAGGGCAAGGTCCACTGTGACTGAGCCCTCA 124
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      5354 ATGGAGACTTGTCTAGCTTTGGGGTGGCCAAGGGCAAGGTCCACTGTGACTGAGCCCTCA 5413

Qy       125 CCTCCACGCCTACCTCATAGCTTCACAGCCTTGCCTTCAGCCTCTGAGCTCCAGGGGTCA 184
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      5414 CCTCCACGCCTACCTCATAGCTTCACAGCCTTGCCTTCAGCCTCTGAGCTCCAGGGGTCA 5473

Qy       185 GCAGCTTAGTGTATCAACAGGGAGTGGATTCACCAAATT 223
             |||||||||||||||||||||||||||||||||||||||
Db      5474 GCAGCTTAGTGTATCAACAGGGAGTGGATTCACCAAATT 5512
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